

and matter that has been added is indicated by underlining. A clean version of the pending claims, as amended, is attached hereto as Exhibit D.

Please amend the claims as follows:

Please amend claims 41, 49, 80-83 and 85-87 to read as follows:

C2 41. (Three Times Amended) A computer system for determining biological pathways involved in the action of a drug in a cell type, said computer system comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising the steps of:

(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;

(c) forming a model drug response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said function by varying the scaling transformations of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the action of said drug in said cell type.

C3 49. (Twice Amended) The computer system of claim 48 wherein the expected probability distribution of minimized determined values of said function is determined by:

C3
Cont'd

- (i) randomizing the drug response with respect to the plurality of levels of drug exposure or randomizing the model drug response by randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;
- (ii) determining a theoretical minimum value of the function by a method comprising:
 - determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or
 - determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and
- (iii) repeating steps (i) through (ii) to determine a plurality of theoretical minimum values,

wherein said plurality of minimum values forms said expected probability distribution of minimized values.

C4

80. (Twice Amended) A computer system for identifying a more pathway specific drug candidate than an initial drug candidate comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs

wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) determining the biological pathways involved in the action of an initial drug candidate by a method comprising:
 - (i) receiving an initial drug response of said initial drug candidate in a cell of a cell type, said initial drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the initial drug candidate,

C4
cont'd

- (ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said initial drug candidate in said cell type,
 - (iii) forming a model initial drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,
 - (iv) determining the value of a function of the difference between said initial drug response and said model initial drug response, and
 - (v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,
- so that the combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the initial drug candidate;
- (b) determining the biological pathways involved in the action of a modified drug candidate, said modified drug candidate having a modified structure of the initial drug candidate, by a method comprising:
 - (i) receiving a modified drug response of said modified drug candidate in a cell of the cell type, said modified drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the modified drug candidate,
 - (ii) forming a model modified drug response as a second combination of the one or more biological pathway responses, wherein each of said

one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

- (iii) determining the value of a function of the difference between said modified drug response and said model modified drug response, and
- (iv) minimizing the determined value of the function of the difference between said modified drug response and said model modified drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the modified drug candidate, and

wherein said modified drug candidate is identified as a more pathway-specific drug candidate than said initial drug candidate if fewer biological pathways are involved in the action of said modified drug candidate than in the action of said initial drug candidate.

81. (Twice Amended) A computer system for identifying one or more specific biological pathways that are involved in the action of a drug and that mediate side-effects of the drug, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) determining the biological pathways involved in the action of a first drug by a method comprising:
 - (i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the first drug,

c4
cont'd

C4
cont'd

- (ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said first drug in said cell type,
- (iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,
- (iv) determining the value of a function of the difference between said first drug response and said model first drug response, and
- (v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;

- (b) determining the biological pathways involved in the action of a second drug, wherein said second drug is different from said first drug and exhibits therapeutic efficacy for the same disease or disorder as said first drug, by a method comprising:
 - (i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,
 - (ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

- c4
cont'd
- (iii) determining the value of a function of the difference between said second drug response and said model second drug response, and
 - (iv) minimizing the determined value of the function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the second drug; and

- (c) identifying specific biological pathways involved in the action of the first drug that are different from those biological response pathways involved in the action of the second drug so that one or more specific biological pathways that are involved in the action of the first drug and that mediate side-effects of the first drug are identified.

82. (Twice Amended) A computer system for identifying one or more specific biological pathways that are involved in mediating therapeutic efficacy for a disease or disorder, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) determining the biological pathways involved in the action of a first drug by a method comprising:
 - (i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the first drug,
 - (ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative

- measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said first drug in said cell type,
- (iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,
 - (iv) determining the value of a function of the difference between said first drug response and said model first drug response, and
 - (v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,
- so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;
- (b) determining the biological pathways involved in the action of a second drug, wherein said second drug is different from said first drug and exhibits therapeutic efficacy for the same disease or disorder as said first drug, by a method comprising:
 - (i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,
 - (ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,
 - (iii) determining the value of a function of the difference between said second drug response and said model second drug response, and

- (iv) minimizing the determined value of the function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the second drug; and

- (c) identifying specific biological pathways involved in the action of both the first and second drugs so that one or more specific biological pathways that are involved in the action of said first drug and mediate therapeutic efficacy for the disease or disorder are identified.

C4
Cont'd

83. (Twice Amended) A computer system for determining biological pathways involved in the action of a drug in a cell type comprising
a process, and
a memory coupled to said processor and encoding one or more programs,
wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of a function of the difference between a provided drug response and a model drug response, wherein:

- (a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;
- (b) said provided drug response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said drug; and

- C4
Cont'd
- (c) said model drug response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the action of said drug in said cell type.

85. (Twice Amended) The computer system of claim 84 wherein the expected probability distribution is obtained by a method comprising:

- C5
- (a) randomizing the drug response with respect to the plurality of levels of drug exposure, or, randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;
 - (b) determining a theoretical minimum value of the function by a method comprising:

determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or

determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and

- (c) repeating steps (a) through (b), so that a plurality of theoretical minimum values is thereby determined,

wherein the plurality of theoretical minimum values forms the expected probability distribution.

86. (Twice Amended) A computer system for determining biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of an objective function of the difference between a received environmental response and a model environmental response, wherein:

- (a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;
- (b) said received environmental response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said environmental change; and
- (c) said model environmental response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the effect of said environmental change upon said cell type.

87. (Twice Amended) A computer system for determining biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs, wherein said one or more programs cause said processor to perform a method comprising the steps of:

- C-5
cont'd
- (a) receiving an environmental response to said environmental change upon said cell type, said environmental response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of exposure to said environmental change;
 - (b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;
 - (c) forming a model environmental response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;
 - (d) determining the value of a function of the difference between said environmental response and said model environmental response; and
 - (e) minimizing said determined value of said function by varying the scaling transformation of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the effect of said environmental change upon said cell type.

Please add new claims as follows:

C-6

88. (New) A computer system for representing measured drug response data of a drug in a cell type, said computer system comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising the steps of: